IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Robert E. Johnson et al.	GROUP ART UNIT:	1644
SERIAL NO.:	10/634,199	CONFIRMATION NO.:	8286
EXAMINER:	Kim, Yunsoo	ATTORNEY DOCKET NO.:	3618/1/US (PC31407)
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TITLE: Formulations of Modified Antibodies and Methods of Making the Same

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE

Dear Sir:

In response to the Office Action mailed on June 14, 2006, with respect to the above-identified application, please consider the following amendments and remarks.

Amendments to the Claims are reflected in the listing of claims which begin on page 2 of this paper.

Remarks/Arguments begin on page 9 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

LISTING OF CLAIMS:

1. (Withdrawn) A method of making an modified antibody formulation, comprising:

    a) providing a pre-lyophilized modified antibody solution comprising molecules capable of adversely affecting the stability or solubility of the modified antibody after lyophilization, and a modified antibody;

    b) removing at least some of the molecules from the pre-lyophilized modified antibody solution; and

    c) lyophilizing the solution from step (b), producing a lyophilized modified antibody formulation.

2. (Withdrawn) The method of claim 1, the modified antibody comprising an antibody fragment covalently attached to at least one nonproteinaceous polymer.

3. (Withdrawn) The method of claim 2, wherein the at least one nonproteinaceous polymer is at least one poly(ethyleneglycol) polymer.

4. (Withdrawn) The method of claim 3, wherein the at least one poly(ethyleneglycol) polymer is at least two methoxypoly(ethyleneglycol) polymers.

5. (Withdrawn) The method of claim 2, wherein the at least one nonproteinaceous polymer is covalently attached to the antibody through a linker.

6. (Withdrawn) The method of claim 5, wherein the linker comprises a succinimide moiety covalently attached to the antibody fragment through a cysteine residue of the antibody fragment.

7. (Withdrawn) The method of claim 6, wherein the linker further comprises a lysine residue that is covalently attached to the succinimide moiety and to the at least one nonproteinaceous polymer.

8. (Withdrawn) The method of claim 1, wherein the modified antibody is CDP870.

9. (Withdrawn) The method of claim 1, the molecules capable of adversely affecting the stability or solubility of the modified antibody after lyophilization provided in step (a) are smaller than the modified antibody.

10. (Withdrawn) The method of claim 1, wherein the molecules are removed in step (b) by dialysis.

11. (Withdrawn) The method of claim 1, wherein the molecules are removed in step (b) by diafiltration.

12. (Withdrawn) The method of claim 1, wherein at least 90% of the molecules are removed in step (b).

13. (Withdrawn) The method of claim 1, wherein the molecules removed in step (b) are salt molecules.

14. (Withdrawn) The method of claim 1, wherein the pre-lyophilized modified antibody solution provided in step (a) further comprises a volatile buffer, the method further comprising exchanging the volatile buffer for a non-volatile physiologically compatible buffer in step (b).

15. (Withdrawn) The method of claim 1, wherein the solution lyophilized in step (c) further comprises at least one excipient to facilitate reconstitution of the lyophilized modified antibody in a reconstitution solution.

16. (Withdrawn) The method of claim 15, wherein the at least one excipient is selected from the group consisting of a surfactant and a sugar.

17. (Withdrawn) The method of claim 1, further comprising a step of reconstituting the lyophilized modified antibody in a reconstitution solution, producing a formulation of reconstituted modified antibody.

18. (Withdrawn) The method of claim 17, wherein the formulation of reconstituted modified antibody has a modified antibody concentration of about 100 mg/ml to about 300 mg/ml.

19. (Withdrawn) The method of claim 17, wherein the formulation of reconstituted modified antibody has a modified antibody concentration of at least about 300 mg/ml to about 450 mg/ml.

20. (Original) An antibody formulation produced according to the method of claim 1.

21. (Withdrawn) A method of making a formulation of CDP870, comprising:

a) providing a pre-lyophilized solution comprising: CDP870 and molecules capable of adversely affecting the stability or solubility of CDP870 after lyophilization ;

b) removing at least some of the molecules from the pre-lyophilized solution; and

c) lyophilizing the solution from step (b), producing a lyophilized CDP870 formulation.

22. (Withdrawn) The method of claim 21, wherein the molecules are removed in step (b) by dialysis.

23. (Withdrawn) The method of claim 1, wherein the molecules are removed in step (b) by diafiltration.

24. (Withdrawn) The method of claim 1, wherein at least 90% of the molecules are removed in step (b).

25. (Withdrawn) The method of claim 1, wherein the molecules removed in step (b) are salt molecules.

26. (Withdrawn) The method of claim 1, wherein the pre-lyophilized solution provided in step (a) further comprises a volatile buffer, the method further comprising exchanging the volatile buffer for a non-volatile physiologically compatible buffer in step (b).

27. (Withdrawn) The method of claim 1, wherein the solution lyophilized in step (c) further comprises at least one excipient to facilitate reconstitution of the lyophilized CDP870 formulation in a reconstitution solution.

28. (Withdrawn) The method of claim 27, wherein the at least one excipient is selected from the group consisting of a surfactant and a sugar.

29. (Withdrawn) The method of claim 1, further comprising a step of reconstituting the lyophilized CDP870 formulation in a reconstitution solution, producing a formulation of reconstituted CDP870.

30. (Withdrawn) The method of claim 29, wherein the formulation of reconstituted CDP870 has a concentration of about 100 mg/ml to about 300 mg/ml CDP870.

31. (Withdrawn) The method of claim 29, wherein the formulation of reconstituted CDP870 has a concentration of at least about 300 mg/ml to about 450 mg/ml CDP870.

32. (Original) A formulation of CDP870 produced according to the method of claim 21.

33. (Withdrawn) A method of treating or preventing a condition or disease in a mammalian subject, comprising:

a) providing a reconstituted lyophilized formulation of CDP870 produced by, prior to lyophilization, removing molecules capable of adversely affecting the stability or solubility of CDP870 after lyophilization; and

b) administering a pharmaceutically effective amount of the reconstituted lyophilized formulation of CDP870 to the subject.

34. (Withdrawn) The method of claim 33, wherein the molecules are removed prior to lyophilization by dialysis.

35. (Withdrawn) The method of claim 33, wherein the molecules are removed prior to dialysis by diafiltration.

36. (Withdrawn) The method of claim 33, wherein the subject is a human being.

37. (Withdrawn) The method of claim 33, wherein the disease treated or prevented according to the method is selected from the group consisting of: primary biliary cirrhosis; Myelodysplastic syndrome; chronic variable immunodefficientcy; treatment refractory sarcoidosis; diffuse lung disease, such as pulmonary fibrosis that is idiopathic or secondary to RA, or acute interstitial pneumonitis; vasculitis, such as Wegeners vasculitis, polyarteritis nodosa, temporal arteritis, IgA

nephropathy (Henoch-Schonlein Purpura); crescentic nephritisjuvenile treatment resistant uveitis; adult treatment resistant uveitis; primary sclerosing cholangitis, alcohol induced hepatitis, ulcerative colitis, inflammatory skin diseases, such as bullous pemhigoid, and pemphigus vulgaris; polyositis (dermatomyositis); or an inflammatory disease, such as endotoxic shock associated with bacterial sepsis or a chronic disease such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, and multiple sclerosis.

38. (Withdrawn) The method of claim 33, wherein the disease treated or prevented according to the method is rheumatoid arthritis.

39. (Original) A high concentration modified antibody formulation, comprising a modified antibody in a diluent for a modified antibody concentration of at least about 300 mg/ml.

40. (Original) The formulation of claim 39, the modified antibody comprising an antibody fragment covalently attached to at least one nonproteinaceous polymer.

41. (Original) The formulation of claim 40, wherein the at least one nonproteinaceous polymer is at least one poly(ethyleneglycol) polymer.

42. (Original) The formulation of claim 41, wherein the at least one poly(ethyleneglycol) polymer is at least two methoxypoly(ethyleneglycol) polymers.

43. (Original) The formulation of claim 40, wherein the at least one nonproteinaceous polymer is covalently attached to the antibody through a linker.

44. (Original) The formulation of claim 40, wherein the linker comprises a succinimide moiety covalently attached to the antibody fragment through a cysteine residue of the antibody fragment.

45. (Original) The formulation of claim 44, wherein the linker further comprises a lysine residue that is covalently attached to the succinimide moiety and to the at least one nonproteinaceous polymer.

46. (Original) The formulation of claim 45, wherein the modified antibody is CDP870.

47. (Original) The formulation of claim 39, wherein the concentration of modified antibody is

about 300 mg/ml to about 450 mg/ml.

48. (Original) The formulation of claim 39, wherein the diluent is an aqueous solution.

49. (Original) The formulation of claim 48, wherein the diluent comprises a buffer that maintains the pH of the antibody formulation from about 4.5 to about 6.0.

50. (Original) The formulation of claim 39, wherein the high concentration modified antibody formulation has been produced by removing at least some molecules capable of adversely affecting the stability or solubility of the modified antibody after lyophilization from a pre-lyophilized modified antibody solution, lyophilizing the solution, and reconstituting the resulting lyophilized modified antibody in an appropriate volume of the diluent to produce the high concentration modified antibody formulation.

51. (Original) The formulation of claim 50, wherein the at least some molecules are removed by dialysis prior to lyophilizing.

52. (Original) The formulation of claim 50, wherein the at least some molecules are removed by diafiltration prior to lyophilizing.

53. (Original) The formulation of claim 39, wherein the high concentration formulation of modified antibody has been produced by concentrating a solution comprising a lower concentration of the modified antibody, by concentrating equilibrium dialysis.

54. (Original) A high concentration formulation of CDP870, comprising CDP870 in a diluent for a CDP870 concentration of at least about 300 mg/ml.

55. (Original) The formulation of claim 54, wherein the concentration of CDP870 is about 300 mg/ml to about 450 mg/ml.

56. (Original) The formulation of claim 54, wherein the diluent is an aqueous solution.

57. (Original) The formulation of claim 54, wherein the diluent comprises a buffer that maintains the pH of the antibody formulation from about 4.5 to about 6.0.

58. (Original) The formulation of claim 54, wherein the high concentration CDP870 formulation

has been produced by removing at least some molecules capable of adversely affecting the stability or solubility of CDP870 after lyophilization from a pre-lyophilized modified antibody solution, lyophilizing the solution, and reconstituting the resulting lyophilized CDP870 in an appropriate volume of the diluent to produce the high concentration CDP870 formulation.

59. (Original) The formulation of claim 58, wherein the at least some molecules are removed by dialysis prior to lyophilizing.

60. (Original) The formulation of claim 58, wherein the at least some molecules are removed by diafiltration prior to lyophilizing.

61. (Original) The formulation of claim 54, wherein the high concentration formulation of CDP870 has been produced by concentrating a solution comprising a lower concentration of CDP870, by concentrating equilibrium dialysis.

REMARKS

Claims 1-61 were pending in the above-identified application prior to entry of this Amendment. In this Amendment, claims 1-19, 21-31, and 33-38 have been withdrawn. Accordingly, after entry of this Amendment, claims 20, 32, and 39-61 are pending in this case. The changes to the claims do not constitute the addition of new matter and full support for the changes may be found in the specification and claims as originally filed.

Restriction Requirement

Examiner has required Applicant to elect one of groups I-III in the Office Action under 35 U.S.C. §121. The claims were separated in the following groups:

Group I: Claims 1-19, 21-31, drawn to a method of making a modified antibody formulation classified in class 424, subclass 179.1.

Group II: Claims 20, 32, 39-61, drawn to an antibody formulation, classified in class 424, subclasses 130.1, and 134.1.

Group III: Claims 33-38, drawn to a method of treating or preventing a condition in a mammalian subject, classified in class 424, subclasses 130.1 and 134.1.

Applicants hereby provisionally elect, with traverse, Group II, claims 20, 32, and 39-61, drawn to an antibody formulation.

Applicant respectfully submits that examination of all pending claims 1-61 of the present application is far less burdensome for both Applicant and Examiner than would be prosecution of potentially 3 separately filed applications as a result of Examiner's restriction.

At a minimum, Applicant respectfully requests that Examiner consolidate the numerous groupings sharing the same classification, particularly those sharing both the same class and subclass. Applicant respectfully submits that such consolidation will impose no serious burden on examination, nor has Examiner alleged that such a burden exists as required under the rules.

The Applicants reserve the right to pursue the remaining claims in divisional or continuation applications. The Applicants note that restriction between product and process claims was required. Further, Applicants note if the elected product claims are found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder.

It is respectfully submitted that the claims have been put in condition for allowance. Notification to this affect is earnestly solicited. The Examiner is encouraged to contact the Applicants' undersigned attorney to discuss this matter if any questions should arise upon further examination of the pending claims.

Respectfully submitted,

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Date

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